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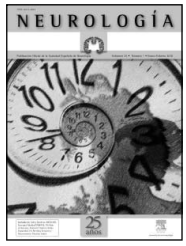

ORIGINAL ARTICLE

New mutation in the *PSEN1* (E120G) gene associated with early onset Alzheimer's disease

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KEYWORDS
Alzheimer's disease;
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Abstract
Objective: To describe a novel mutation in exon 5 of the presenilin 1 gene (E120G) associated with early-onset autosomal dominant Alzheimer's disease (AD).
Patient and methods: The proband was a man who began with memory loss and progressive cognitive decline at the age of 34. His father and his sister suffered from early-onset cognitive decline. The genetic study performed on the blood sample using the single strand conformation polymorphism (SSCP) technique did not detect any abnormality suggestive of the presence of a mutation in *PSEN1, PSEN2,* and *APP*. In the last stage of the disease the patient had seizures and gait alteration. He died at the age of 44. Coding exons 3-12 of *PSEN1* were studied by direct sequencing using isolated DNA from frozen brain tissue of the proband.
Results: The neuropathological examination showed the presence of frequent amyloid plaques and neurofibrillary tangles and severe amyloid angiopathy. The direct sequencing of the *PSEN1* gene disclosed the presence of the E120G mutation.
Conclusions: E120G is a novel mutation in *PSEN1* that probably causes early-onset autosomal dominant AD. Absence of genetic alterations in screening techniques (SSCP) does not rule out the presence of mutations. We recommend direct sequencing for the genetic study of patients with early-onset autosomal dominant AD.

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PALABRAS CLAVE
Enfermedad de Alzheimer;
Presenilina 1;
Demencia de inicio precoz;
Mutación;
Demencia familiar

Nueva mutación en el gen *PSEN1* (E120G) asociada a enfermedad de Alzheimer de inicio precoz

Resumen
Objetivo: Describir una nueva mutación en el exón 5 del gen *PSEN1* (E120G) asociada a enfermedad de Alzheimer (EA) de inicio precoz y patrón de herencia autosómico dominante.
Paciente y métodos: El probando era un varón en el que se inició la enfermedad a los 34 años con problemas de memoria y deterioro cognitivo progresivo. Su padre y una hermana presentaron deterioro cognitivo de inicio precoz. El estudio genético por *single strand conformation polymorphism* (SSCP) de una muestra sanguínea del probando no detectó anormalidades que indicaran mutaciones en *PSEN1, PSEN2* y *APP*. En los estadios finales de la enfermedad, el paciente presentó crisis epilépticas y alteración de la marcha. El paciente falleció a los 44 años. Los exones 3-12 del gen *PSEN1* fueron analizados por secuenciación directa utilizando ADN aislado del tejido cerebral congelado del probando.
Resultados: El examen neuropatológico reveló abundantes placas seniles y ovillos neurofibrilares, junto con una angiopatía amiloidea severa. El nuevo estudio genético del gen *PSEN1* realizado mediante secuenciación directa detectó la mutación E120G.
Conclusiones: E120G es una nueva mutación en *PSEN1,* probable causa de EA de inicio precoz con patrón autosómico dominante. La ausencia de mutaciones en estudios genéticos de cribado (SSCP) no descarta que haya mutaciones. Se recomienda el estudio genético mediante secuenciación directa en los casos de EA de inicio precoz y patrón de herencia autosómico dominante.

Introduction

So far three genes have been implicated in causing monogenic Alzheimer's disease (AD), which is characterised by an early onset and an autosomal dominant inheritance pattern[1]. These three genes are the amyloid precursor protein (APP), presenilin 1 gene (PSEN1) and presenilin 2 gene (PSEN2). Mutations in the *PSEN1* gene are those that most often cause early-onset AD with autosomal dominant pattern, since 177 pathogenic mutations have been reported in it so far[2]. The clinical phenotype of patients with *PSEN1* mutations is similar to that seen in sporadic AD with an earlier onset age (average, 44 years), although cases have been reported with a particular phenotype (AD and spastic paraparesis, frontal variant of frontotemporal lobar degeneration, AD associated with lobar haematomas, etc.)[3-5].

In this study, we describe a new mutation in exon 5 of *PSEN1* in a patient with early-onset AD and autosomal dominant pattern.

Patient

Male, 39 years, derived to the information and genetic counselling program for monogenic dementias (PICOGEN) in the Unitat d'Alzheimer i altres trastorns cognitius (UATC) unit at the Hospital Clinic in Barcelona to assess a genetic study[6]. Right-handed, schooled until age 14, alcohol consumption 20 g/day, frequent user of cannabis without dependence criteria and smoker, with no other relevant medical history. His wife related that the patient presented the first cognitive problems at age 34 in the form of forgetting errands and recent information, with some episodes of disorientation in public transport. A neuropsychological study later showed diffuse cognitive impairment with frontal and temporal predominance. The clinical diagnosis was probable AD in stage 4 of the Global Deterioration Scale (GDS), and pharmacological treatment with donepezil was started. At the time of his UATC visit, the patient was still independent for basic activities of daily living, although he presented an obvious amnesia problem (shaving three times a day) and never left his home alone for fear of getting lost.

The family history showed an early onset dementia with an autosomal dominant inheritance pattern. The ages at onset in the father and a sister of the affected patient are not well known, but they died at 54 and 49 years, respectively, after a clinical picture of cognitive decline for several years.

The initial examination showed no neurological focus. Cranial computed tomography (CT) did not offer significant findings and cerebral single photon emission CT (SPECT) showed a discreet left temporoparietal hypoperfusion.

After a session of genetic counselling and signing the informed consent, blood was collected. We analysed exons 3-12 of *PSEN1* and *PSEN2* and exons 16 and 17 of *APP* through single-strand conformation polymorphism (SSCP), but did not detect any abnormalities that indicated genetic alterations in these genes.

During monitoring, the patient presented progressive cognitive and motor impairment, with onset of behavioural disturbances (loss of initiative, depressive symptoms,

irritability, hyperactivity and occasional heteroaggressiveness). The patient showed high sensitivity to the side effects of antipsychotic drugs, with axial dystonia. Echolalia and substance usage behaviours appeared at later stages. At that time, the neurological examination showed hyperreflexia and hypertonia/spasticity with right predominance, primitive reflexes of the midline and frontal liberation and gait disturbance. In the final period, the patient presented loss of ambulation, severe dysphagia, cachexia and seizures. The patient died at age 44 after 10 years of disease. The family of the patient donated the brain to the neurological tissue bank at the Hospital Clinic-University of Barcelona.

Methods

A neuropathological study of the patient was performed using haematoxylin-eosin staining and immunohistochemical detection of amyloid βA4, phosphorylated tau protein (AT-8), alfasynucleín and TDP-43. DNA was extracted from frozen brain tissue using DNeasy tissue kit (Qiagen). Exons 3-12 of the *PSEN1* gene were analysed by direct sequencing according to prior descriptions[7].

Results

Neuropathological study

Brain of 950 g. The macroscopic study observed a marked general atrophy. In the microscopic study there were numerous senile plaques, diffuse and mature, with immunoreactivity for βA4, diffusely distributed throughout the brain, the brainstem and the cerebellum (Fig. 1). Along with the senile plaques, widespread immunoreactivity was present for phosphorylated tau protein, in neurons with abundant neurofibrillary degeneration, neuritic plaques and neuropil threads (Fig. 1). Absence of reactivity to alfasynucleín and TDP43. Severe amyloid angiopathy in leptomeningeal and intracortical vessels, cerebral and cerebellar. The final pathologic diagnosis was AD in Braak stages VI/VI with neurofibrillary degeneration and Braak stage C amyloid deposits with associated severe amyloid angiopathy.

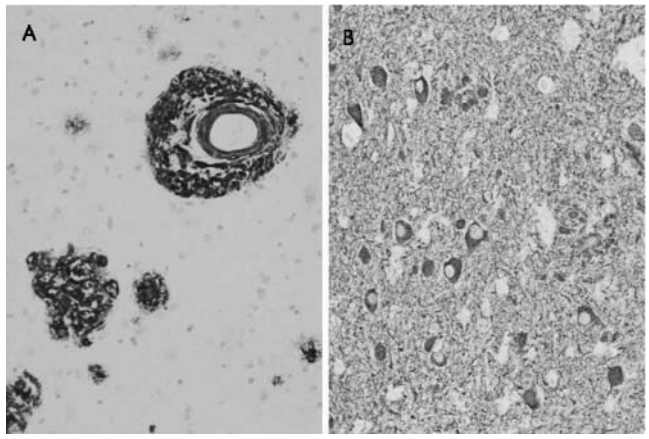

Figure 1 A: βA4 amyloid; cerebral amyloid angiopathy and plaques; the amyloid deposits of the brain parenchyma appear to spread from the vessel wall; diffuse and mature amyloid plaques can also be observed. B: phosphorylated tau protein; neurofibrillary degeneration in the cytoplasm of neurons and in numerous cellular processes or neuropil threads next to neuritic plaques.

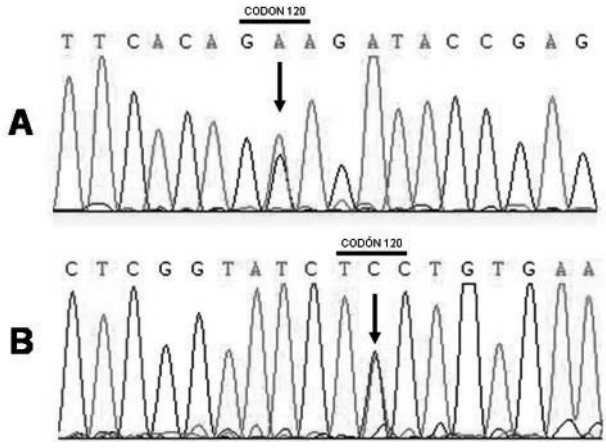

Figure 2 DNA sequence of exon 5 of *PSEN1* showing the E120G mutation (arrow). A: direct sequence. B: inverse sequence.

Genetic study

We found one nucleotide change (A>G) in exon 5 of the *PSEN1* gene. This genetic alteration leads to an amino acid change at codon 120 of glutamate (GAA) to glycine (GGA), leading to the E120G mutation (Fig. 2). No cosegregation studies of the mutation could be performed in this family, since there were no other living affected relatives, nor was there brain tissue available from deceased affected relatives.

Discussion

The E120G mutation is located in the first hydrophilic region connecting transmembrane domains 1 and 2, in a highly conserved codon in *PSEN1* and *PSEN2*[8]. This fact, together with the familiar presentation of the disease, confirmation of AD in the pathological study and the previous description of other mutations in the same codon (E120K, E120D)[8,9], indicates that this mutation is the cause of the disease in this patient, and it is unlikely to be a rare non-pathogenic polymorphism. However, it has not been possible to carry out cosegregation or functional studies to confirm causality. In this sense, according to a recent article by Guerreiro et al[10] that assesses the degree of pathogenicity attributable to genetic changes detected in genes *PSEN1* and *PSEN2*, this mutation would have to be attributed a pathogenicity with a degree of "likely".

The E120G mutation, like most of the mutations described in this gene, leads to early-onset AD with an autosomal dominant inheritance pattern. The early age of onset in this

patient is similar to that described in another mutation in the same codon (range of age of onset in mutation E120K, 32-39 years) and a decade less than the other mutation described in this codon (41-53 years)[8,9]. Epileptic crises have been reported in various mutations of the *PSEN1* gene, including mutation E120D. The pathology includes the typical findings of AD along with significant amyloid angiopathy.

The technical approach for the detection of mutations in candidate patients can be handled in different ways, depending on the availability of laboratory diagnostic techniques. Direct sequencing study has a higher sensitivity than conventional SSCP study (estimated sensitivity of around 80%, depending on the specific laboratory), although the latter is often used as an initial screening method for its lower economic and time costs. After this test, those fragments that show anomalous patterns are then sequenced[11]. Thus, the clinician should be aware of the SSCP study sensitivity when reporting the results to the patients and/or their families. The existence of false negatives in the SSCP study must make the clinician reconsider the request for a new genetic study by direct sequencing in cases with high probability of having a mutation causing AD in which a prior SSCP study has proven negative[5]. The case described emphasises the importance of carrying out sequencing studies in cases of early-onset AD and autosomal dominant inheritance pattern, even though the study by less sensitive conventional screening techniques is negative. However, it must be stressed that none of these techniques allows an assessment of gene dosage, that is, the presence of deletions or duplications of the entire gene.

In summary, we describe a new mutation in the PSEN1 gene (E120G) that is the probable cause of early-onset AD with an autosomal dominant inheritance pattern. This case emphasises the importance of carrying out genetic studies with direct sequencing techniques in compatible cases, even in cases which return negatives in less sensitive techniques.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Campion D, Dumanchin C, Hannequin D, Dubois B, Belliard S, Puel M, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet. 1999;65:664-70.
2. Alzheimer disease & frontotemporal dementia mutation database. Available at: http://www.molgen.ua.ac.be/admutacions/
3. Ataka S, Tomiyama T, Takuma H, Yamashita T, Shimada H, Tsutada T, et al. A novel presenilin-1 mutation (Leu85Pro) in early-onset Alzheimer disease with spastic paraparesis. Arch Neurol. 2004;61:1773-6.
4. Queralt R, Ezquerra M, Lleo A, Castellvi M, Gelpi J, Ferrer I, et al. A novel mutation (V89L) in the presenilin 1 gene in a family with early onset Alzheimer's disease and marked behavioural disturbances. J Neurol Neurosurg Psychiatry. 2002;72:266-9.
5. Sánchez-Valle R, Lladó A, Ezquerra M, Rey MJ, Rami L, Molinuevo JL. A novel mutation in the PSEN1 gene (L286P) associated with familiar dementia of Alzheimer type and lobar haematomas. Eur J Neurol. 2007;14:1409-12.
6. Molinuevo JL, Pintor L, Peri JM, Lleó A, Oliva R, Marcos T, et al. Emotional reactions to predictive testing in Alzheimer's disease and other inherited dementias. Am J Alzheimer Dis. 2005;20:233-8.
7. Cruts M, Van Duijn CM, Backhovens H, Van den Broeck M, Wehnert A, Serneels S, et al. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. Hum Mol Genet. 1998;7:43-5.
8. Poorkaj P, Sharma V, Anderson L, Nemens E, Alonso ME, Orr H, et al. Missense mutations in the chromosome 14 familial Alzheimer's disease presenilin 1 gene. Hum Mutat. 1998;11:216-21.
9. Hutton M, Busfield F, Wragg M, Crook R, Perez-Tur J, Clark RF, et al. Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. Neuroreport. 1996;7:801-5.
10. Guerreiro RJ, Baquero M, Blesa R, Boada M, Brás JM, Bullido MJ, et al. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol Aging. 2008 Jul 28 [Epub ahead of print].
11. Hayashi K, Yandell DW. How sensitive is PCR-SSCP? Hum Mutat. 1993;2:338-46.